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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/489,394	01/21/2000	Vanessa Hsei	P1085R6	5782

9157 7590 05/06/2005

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 05/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/489,394	HSEI ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *124-133* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *124-133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/14/05 has been entered.

2. Claim 124 has been amended.

Claim 133 has been added.

3. Claims 124-133 are pending and under examination..

4. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

5. The following Office Action contains NEW GROUNDS of rejections.

Specification

6. The specification is objected to for the following reason:

a. The first line of the specification needs to be updated to indicate that application 09/355014 is now US Patent 6,870033 and application 09/012116 is abandoned.

Rejections Withdrawn

7. The rejection of Claims 124-132 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 20, 25, 26, 28, 31, 32-36 of copending Application No. 09/726,258 in view of Carter et al (Antibody Engineering, A practical approach, IRL Press, chapter 13, pages 291-308, 1996, IDS #8) and Allan et al (U.S. Patent 5,620,689, filed 6/95) is withdrawn in view of the TD filed.

8. The rejection of claims 124-132 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 27 of copending Application No. 09/355,014 in view of Carter et al (Antibody Engineering, A practical approach, IRL Press, chapter 13, pages 291-308, 1996, IDS #8) and Allan et al (U.S. Patent 5,620,689, filed 6/95) is withdrawn in view of the TD filed.

9. The rejection of claims 124-130 under 35 U.S.C. 103(a) as being unpatentable over Gonzalez et al (U.S.Patent 6,133,426, priority to 1/22/98) and further in view of Zapata et al (FASEB J. 9:A1476, 1995, IDS #8) is withdrawn in view of the updated priority claim.

10. The rejection of claims 124-130 under 35 U.S.C. 103(a) as being unpatentable over Faanes et al (U.S. Patent 5,695,760, filed 4/24/95, IDS #8) and further in view of Zapata et al (FASEB J. 9:A1476, 1995, IDS #8) and Braxton (US Pat. No. 5,766,897, IDS #8) is withdrawn in view of the amendments to the claims but could be reinstated with removal of the newly added limitation (see below).

11. The rejection of claims 124-132 under 35 U.S.C. 103(a) as being unpatentable over Faanes et al (U.S. Patent 5,695,760, filed 4/24/95, IDS #8) in view of Zapata et al (FASEB J. 9:A1476, 1995, IDS #8) and Braxton (US Pat. No. 5,766,897, IDS #8) as applied to claims 124-130 above and further in view of Carter et al (Antibody Engineering, A practical approach, IRL Press, chapter 13, pages 291-308, 1996, IDS #8) and Allan et al (U.S. Patent 5,620,689, filed 6/95) is withdrawn in view of the amendments to the claims but could be reinstated with removal of the newly added limitation (see below).

12. The rejection of claims 124-132 under 35 U.S.C. 103(a) as being unpatentable over Koumenis et al (Protein Science 7(suppl.1):73 7/1998) and further in view of Carter et al (Antibody Engineering, A practical approach, IRL Press, chapter 13, pages 291-308, 1996, IDS #8) and Allan et al (U.S. Patent 5,620,689, filed 6/95) is withdrawn in view of the amendments to the claims but could be reinstated with removal of the newly added limitation (see below).

The Following are New GROUNDS of rejections

Claim Rejections - 35 USC § 112

13. Claims 125-133 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 124-133 are indefinite for reciting "wherein a disulfide bridge is avoided by substituting another amino acid for the corresponding cysteine residue in the opposite chain" in claims 124 and 133 because the exact meaning of the phrase is unclear. Is the disulfide bridge avoided in the hinge or in some other part of the molecule such as the heavy and light chain or somewhere else?

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 124-133 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

Claims 124 and 133 recite the limitation "modified by one or two nonproteinaceous polymer molecules at a free sulfhydryl group of a cysteine residue within the hinge region of the antibody fragment, wherein a disulfide bridge is avoided by substituting another amino acid for the corresponding cysteine residue in the opposite chain". Support for the limitation is stated to be at page 51, 56, 66, 68, and column 15, 16, 19, 20, and elsewhere in the US Patent 6,133,426 as stated in the response at page 6 of the response filed 2/14/05. The response has been carefully considered but is deemed not to be persuasive. The recited passages are directed to polymer fragments with MW of 500kD and 8 fold over the effective size, and polymers of at least 20kD, cysteines residues not in a disulfide bridge are engineered into a site, and cysteine engineered into a hinge for coupling. The patent also states no more than one polymer coupled to a cysteine in the light or heavy chain that would ordinarily form a disulfide bond wherein the disulfide bond is avoided by substituting another amino acid for the cysteine in the opposite chain (see column 22, lines 10-17). The recited passages do not support the claims of a cysteine in the hinge being used for coupling and substituting another amino acid in the opposite chain. The specification and the patent support adding a polymer to a hinge cysteine or to a heavy or light chain cysteine

and substitution of another amino acid for the cysteine in the opposite heavy or light chain. There is no support for the combination of a polymer in a cysteine in the hinge and substitution in the heavy or light chain as broadly claimed. Applicant is required to provide specific support for the limitations in the specification as originally filed or remove them from the claims.

16. Claims 124-133 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody fragment that is modified by one or two PEG molecules at a free cysteine residue within the hinge, wherein the apparent molecular weight on size exclusion chromatography is about 500 or 800 or 1800 kD and has an average PEG of 20 or 30 kD and the conjugate is apparently 8 fold greater than the parent fragment where in the conjugate binds an antigen which can be HER2 or CD20, does not reasonably provide enablement for a conjugate that does not bind any antigen or HER2 or CD20 or a conjugate wherein the polymer is conjugated to a cysteine in the light or heavy chain or no polymer is attached and the cysteine in the opposite chain is substituted by another amino acid to avoid a disulfide bond between the light and heavy chains. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They

include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to any antibody fragment that has the hinge cysteine conjugated and wherein the heavy and light chains are linked by a disulfide bond and in the antibody fragment the cysteine in the heavy or light chain is substituted for any amino acid and the free cysteine does not have a polymer attached.

The specification teaches a general method for covalent attachment of a nonproteinaceous polymer to a cysteine residue in the hinge, however, the specification does not enable the production of a functional antigen binding fragment as broadly claimed wherein only the cysteine in the hinge has polymer and the free cysteine in the heavy or light chain does not.

The specification does not enable the replacement of the cysteine residue with just any amino acid. One skilled in the art would conclude that not every amino acid, especially those that have bulky side chains, would be tolerated and result in proper folding and packing of the heavy and light chains in the absent of the disulfide bond in the antibody. In addition, the specification fails to teach an example where the disulfide bond linking the cysteine residues in the light or heavy chain is substituted for an amino acid and the cysteine is covalently coupled to a nonproteinaceous polymer that results in a functional antibody. As evidenced by Cruse et al, (Illustrated Dictionary of

Immunology, CRC Press, page 107, 1995), the disulfide bond in a Fab' fragment is between the heavy and light chains and has hinge cysteines. As such replacement of one of the heavy or light chain cysteines would produce a fragment with a free cysteine in the heavy or light chain and in the hinge and one skilled in the art would conclude that covalent attachment of a nonproteinaceous polymer at a site away from the hinge region would result in altered packing of the heavy and light chains and thus would not produce an antigen binding fragment. In addition, the specification does not teach specifically conjugating at the hinge over the free cysteine in the heavy or light chain. Thus, how would one avoid specific conjugation to the hinge and not the free cysteine in the heavy or light chain? In addition, a molecule that is modified at both sites is not taught in the prior art or the specification that binds any antigen.

Thus, undue experimentation would be require to make and use the instantly claimed antibody fragments.

Conclusions

17. No Claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30

am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Siew, can be reached at (571) 272-0787.

19. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 703-872-9306.

Respectfully,

Larry R. Helms Ph.D.

571-272-0832

LARRY R. HELMS, PH.D
PRIMARY EXAMINER